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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,090	12/14/1999	AXEL ULLRICH	2923-0347	3321

6449 7590 11/16/2004

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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/461,090	ULLRICH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-31 and 33-38* is/are pending in the application.

4a) Of the above claim(s) *37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-31,33-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on July 12, 2004 has been entered. The claims pending in this application are claims 22-38 wherein claim 37 has been withdrawn from consideration as being directed to a non-elected invention. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on July 12, 2004. Claims 22-31, 33-36, and 38 will be examined.

Response to Arguments

In page 7, second paragraph of applicant's remarks, applicant argues that "[T]he office action indicates that claim 37 has been withdrawn from consideration. Applicants contend that claim 37 should be examined because previous claim 32 was canceled in favor of claim 37. Claim 32 recited a second cell and depended from claim 22 which recites the first cell. Claim 32 encompassed a method where the cells were in contact with each other. In view of this, applicants request that claim 37 be examined in the present application".

The above arguments have been fully considered and have not been found persuasive such that claim 37 will be examined. First, since canceled claim 32 requires a second cell which is different from the cell containing the receptor tyrosine kinase while claim 37 requires a second cell having a receptor tyrosine kinase, this indicates that the second cell recited in canceled claim 32 is different from the second cell recited in claim 37. Second, canceled claim 32 does not require that the first cell is in contact with the second cell. Therefore, claim 37 is considered as an independent or distinct from the invention originally claimed and has not been included in previous and this office actions.

Claim Objections

2. Claim 22 is objected to because of the following informalities: "a receptor tyrosine" should be "a receptor tyrosine kinase".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 22-31, 33, 34, 36, and 38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Although the specification describes G protein mediated signal transduction and G-protein-coupled receptors (see specification, page 1), the specification does not adequately describe that G protein coupled receptor initiated extracellular signal pathway recited in claims 22-31, 33, 34, and 36. MPEP 2163.06 states that "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." In view of the embodiments adequately description in the specification, the subject application does not reasonably convey to one skilled in the art that applicant was in possession of the full scopes of

products encompass in the claims at the time of the application was filled. Therefore, the written description requirement has not been satisfied.

In support of this position, attention is directed to the decision of *Vas-Cath inc. V. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 U.S.C. 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Response to Arguments

In page 8, first paragraph of applicant's remarks, applicant argues that "[A]pplicants respectfully disagree and point out page 17, lines 2-9, of the specification which indicates that in the signal pathway, a ligand activates the G protein by interacting with a G protein coupled receptor which produces an intracellular signal that induces the extracellular activity which results in the processing of a transmembrane growth factor precursor and release of the mature factor which interacts with the receptor leading to autophosphorylation and signal generation. Applicants also point out the examples on pages 10-11 and 11-12 and figures la-e and 2a-c which describe a G protein coupled receptor initiated extracellular signal pathway. In view of this disclosure, applicants request that this rejection be withdrawn".

The above arguments have been fully considered and have not been found persuasive to withdraw the rejection. In page 17, lines 2-9, of the specification only describes that "a ligand activates heterotrimeric G-proteins by interaction with a GPCR which results in an intracellular signal that induces the extracellular activity of a transmembrane metalloproteinase. This then

results in extracellular processing of a transmembrane growth-factor precursor and release of the mature factor which, directly or via the proteoglycan matrix, interacts with the ectodomain of the EGFR leading to intracellular autophosphorylation and signal generation". This only suggests that extracellular activity is related a transmembrane metalloproteinase and the specification does not describe that extracellular activity of a transmembrane metalloproteinase is related to G protein coupled receptor initiated extracellular signal pathway which does not describe in the specification. Furthermore, applicant does not indicate, in page 17, lines 2-9 and pages 10-12 of the specification, where has a term "G protein coupled receptor initiated extracellular signal pathway".

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 35 is rejected as vague and indefinite. Although the claim is directed to a method for identifying compounds for modulating G-protein mediated signal transduction, there is no method step for identify compounds for modulating G-protein mediated signal transduction and the goal of the method (preamble) does not match with the method steps of the claim. Please clarify.

Response to Arguments

In page 9, second paragraph of applicant' remarks, applicant argues that the amendment has overcome the rejection.

The above argument has been fully considered and it has not been found persuasive to withdraw the rejection because added phrase "as an indication of said test compound's ability to modulate G-protein mediated signal transduction" is not considered as an identifying step.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 22-26, 28-31, 33-36, and 38 are rejected under 35 U.S.C. 102(a) as being anticipated by Dong *et al.*, (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

Dong *et al.*, teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor.

Regarding claims 22, 23, 33, and 34, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway and claim 22 does not require that stimulating step must be performed before contacting step, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway as recited in claim 22. Since

Dong *et al.*, teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see Figure 4, column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF. Therefore, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application), Dong *et al.*, disclose stimulating G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) as recited in claim 22 wherein said tyrosine kinase is EGFR as recited in claims 23, 33, and 34.

Regarding claims 24-26 and 28-31, since Dong *et al.*, teach that ligands such as EGF that activate the epidermal growth factor receptor (EGFR) are synthesized as membrane-anchored precursors that are proteolytically released by members of the ADAM family of metalloproteases and batimastat is a metalloproteinase inhibitor that prevents EGFR ligand such as EGF release by abolish biological activity of the metalloproteinases (see page 6235, abstract and right column, and page 6239, right column, last paragraph), Dong *et al.*, disclose said compound (ie., batimastat) affecting the G protein or the G protein coupled receptor initiated extracellular signal pathway affects a proteinase (ie., a metalloproteinase) cleaving a precursor of a ligand (ie., the

precursor of EGF) for the receptor tyrosine kinase (ie., EGFR) as recited in claim 24 wherein the compound (ie., batimastat) affects the proteinase (ie., metalloproteinase) by directly inhibiting proteinase activity as recited in claim 25, wherein said precursor of a ligand (ie., the precursor of EGF) is a membrane associated molecule as recited in claim 26, wherein said proteinase is a metalloproteinase as recited in claim 29, and said proteinase activity (ie., biological activity of the metalloproteinase) is inhibited by batimastat as recited in claim 31. Since Dong *et al.*, teach that EGF is proteolytically released from its membrane-anchored precursor by members of the ADAM family of metalloproteases (see page 6235,abstract) and it is known that the ADAM family of metalloproteases are zinc-dependent proteinases (see the specification, page 3, first paragraph), Dong *et al.*, disclose said proteinase (ie., one of the ADAM family of metalloproteases taught by Dong *et al.*,) is a membrane-associated proteinase as recited in claim 28 and said metalloprotease (ie., one of the ADAM family of metalloproteases taught by Dong *et al.*,) is a zinc-dependent proteinase as recited in claim 30.

Regarding claim 35, Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application) and Dong *et al.*, teach that batimastat decreases level of EGFR tyrosine phosphorylation in the HMEC cells (see page 6238, right column and Figure 4), Dong *et al.*, disclose contacting a cell containing a receptor tyrosine kinase (ie., a HMEC cell) capable of activation by G-protein mediated signal transduction with a test compound (ie., batimastat) as

recited in the claim. Since Dong *et al.*, teach that batimastat is a selective metalloprotease inhibitor that prevents EGFR ligand release (see page 6235, abstract and right column, and page 6239, right column, last paragraph) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway, Dong *et al.*, disclose a test compound suspected of being a modulator (ie., batimastat) of a proteinase (ie., a selective metalloprotease) or a precursor of a ligand (ie., the precursor of EGF) of the receptor tyrosine kinase (ie., EGFR) as recited in the claim. Since Dong *et al.*, teach to compare the level of EGFR tyrosine phosphorylation of the HMEC in the presence of batimastat, antagonist mAb225 or EGF (see Figure 4), Dong *et al.*, disclose evaluating G-protein mediated receptor tyrosine kinase (ie., EGFR) activation upon exposure of the cell (ie., the HMEC cells) to said test compound (ie., batimastat) as an indication of said test compound's ability (ie., with or without ability) to modulate G-protein mediated signal transduction as recited in the claim.

Regarding claim 36, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway and claim 36 does not require that stimulating step must be performed before contacting step, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway as recited in claim 36. Since Dong *et al.*, teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF.

Therefore, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application), Dong *et al.,* disclose stimulating G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) wherein said tyrosine kinase is EGFR as recited in claim 36. Since it is known that EGFR has an extracellular domain and a cell comprising EGFR has a G-protein mediated signal transduction pathway wherein EGFR activation occurs by tyrosine phosphorylation of EGFR (see the specification, page 1, last paragraph, and page 2, second paragraph), Dong *et al.,* disclose that said receptor tyrosine kinase is EGFR and said cell (ie., the HMEC cell) comprising the extracellular domain of EGFR and having a G-protein mediated signal transduction pathway wherein one or more tyrosine residues are phosphorylated based on the activation of said protein mediated signal transduction pathway as recited in claim 36. Since Dong *et al.,* teach that EGF is generated from its membrane-anchored precursor by one of the ADAM family of metalloproteases (see page 6235, abstract) and it is know that EGF binds to the extracellular domain of EGFR, Dong *et al.,* disclose that the extracellular domain of said receptor (ie., EGFR) is capable of binding to its receptor ligand (ie., EGF) and said ligand is generated from a

precursor of said ligand (ie., the precursor of EGF) by a proteinase-dependent cleavage (ie., one of the ADAM family of metalloproteases) as recited in claim 36.

Regarding claim 38, since Dong *et al.*, teach to incubate HMEC cells with batimastat or antagonist mAb225 for 24 hr and then treat the HMEC cells with EGF for 20 min (see page 6238, right column and Figure 4) and there is no evidence to show that batimastat can not affect a G protein or G protein coupled receptor initiated extracellular signal pathway and claim 22 does not require that disturbing step must be performed before contacting step, Dong *et al.*, disclose contacting a cell with a compound (ie., batimastat) affecting a G protein or G protein coupled receptor initiated extracellular signal pathway as recited in claim 38. Since Dong *et al.*, teach that the inhibitory effect of batimastat on EGFR tyrosine phosphorylation of the HMEC cells is totally reversed by EGF (see Figure 4, column 5 in the presence of batimastat +EGF), batimastat has no effect on EGFR tyrosine phosphorylation of HMEC cells in the presence of EGF. Therefore, comparing with batimastat treated HMEC cells, the HMEC cells treated with batimastat +EGF has an increased level of EGFR tyrosine phosphorylation (see page 6238, right column and Figure 4). Since it is known that increased level of EGFR tyrosine phosphorylation in a cell indicates that a G protein or G protein coupled receptor initiated extracellular signal pathway of the cell has been activated (for evidence, see claim 36 of this instant application), Dong *et al.*, disclose disturbing G protein mediated signal transduction in a cell (ie., treating the HMEC cells with batimastat+EGF) having a receptor tyrosine kinase (ie., EGFR) wherein the receptor tyrosine kinase is activated and thereby modulating the receptor tyrosine kinase activation by G-protein-mediated signal transduction (ie., increasing the level of EGFR tyrosine phosphorylation) as recited in claim 38.

Therefore, Dong *et al.*, teach all limitations recited in claims 22-26, 28-31, 33-36 and 38.

Response to Arguments

In page 8, last paragraph bridging to page 11, first paragraph of applicant's remarks, applicant argues that: (1) "[A]pplicants point out that Dong et al. does not stimulate/disturb the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims. The office action erroneously indicates that Dong et al. contains all of the features required for stimulating a GPCR initiated extracellular signal pathway. For example, the office action contends that by the administration of batimastat and EGF as disclosed by Dong et al. a G protein or GPCR initiated extracellular signal transduction pathway is activated. This is incorrect. Batimastat is an inhibitor of EGFR tyrosine phosphorylation and, thus, **cannot stimulate the G protein/GPCR mediated signal transduction pathway**. In addition, as shown in the present application (Fig. 4c), exogenous EGF is not capable of stimulating cleavage of Pro-HB-EGF to give HB-EGF and, thus, has no effect on the G protein mediated signal transduction pathway"; (2) "[T]he conclusion in the office action that batimastat plus EGF together increase tyrosine phosphorylation of EGFR is completely wrong. According to Dong et al. batimastat inhibits basal EGFR activity not EGFR activity stimulated by exogenous EGF. Therefore, the addition of both substances leads to increased EGFR activity, whereby the latter is caused only by EGF and thus, has nothing to do with influencing the G protein/GPCR signal transduction pathway. The logic used in the office action is contradictory in itself in that batimastat, on the one hand, blocks EGFR tyrosine phosphorylation, however, on the other hand, together with EGF is used to activate EGFR tyrosine phosphorylation. This means that the feature of stimulation of a G protein or GPCR mediated extracellular signal transduction

pathway was not achieved by batimastat alone, by EGF alone nor by batimastat plus EGF and thus, is not disclosed by Dong et al. The two-stage process of the present invention (activating a receptor tyrosine kinase by stimulating/disturbing the G protein/GPCR mediated pathway and modulating the receptor tyrosine kinase activation by contacting the cell with a compound affecting a G protein/GPCR initiated extracellular signal pathway) is neither explicitly nor inherently disclosed by Dong et al. Dong et al. is not concerned with a G protein or GPCR initiated signal transduction pathway and Dong et al. does not stimulate/disturb the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims. Contrary to statements made in the office action, Dong et al. does not disclose all of the steps in the presently claimed process and thus does not inherently anticipate the presently claimed invention".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, applicant argues that a G protein or GPCR initiated extracellular signal transduction pathway is activated by the administration of batimastat and EGF is incorrect since batimastat is an inhibitor of EGFR tyrosine phosphorylation and cannot stimulate the G protein/GPCR mediated signal transduction pathway. Since Dong *et al.*, teach that batimastat has no direct effect on EGFR activation but appears to work by inhibiting ligand release (see page 6238, right column, second paragraph), a G protein or GPCR initiated extracellular signal transduction pathway is activated by the administration of batimastat and EGF is correct. Note that the claims do not required that a G protein or GPCR initiated extracellular signal transduction pathway is activated by the administration of batimastat alone. Second, although exogenous EGF is not capable of stimulating cleavage of Pro-HB-EGF to give

HB-EGF, note that the claims do not require that the G protein mediated signal transduction pathway must correlate with cleavage of Pro-HB-EGF. Third, applicant argues that the conclusion in the office action that batimastat plus EGF together increase tyrosine phosphorylation of EGFR is completely wrong since batimastat inhibits basal EGFR activity not EGFR activity stimulated by exogenous EGF. Since Dong *et al.*, teach that batimastat has no direct effect on EGFR activation but appears to work by inhibiting ligand release and EGF increases tyrosine phosphorylation of EGFR (see page 6238, right column and Figure 4), the statement "batimastat plus EGF together increase tyrosine phosphorylation of EGFR" is correct. Furthermore, applicant appears to agree with the examiner since she states that "the addition of both substances leads to increased EGFR activity, whereby the latter is caused only by EGF" (see applicant's remarks, page 10, second paragraph). Fourth, applicant argues that "[T]he logic used in the office action is contradictory in itself in that batimastat, on the one hand, blocks EGFR tyrosine phosphorylation, however, on the other hand, together with EGF is used to activate EGFR tyrosine phosphorylation. This means that the feature of stimulation of a G protein or GPCR mediated extracellular signal transduction pathway was not achieved by batimastat alone, by EGF alone nor by batimastat plus EGF and thus, is not disclosed by Dong et al.". Since Dong *et al.*, teach that batimastat has no direct effect on EGFR activation but appears to work by inhibiting ligand release and EGF increases tyrosine phosphorylation of EGFR while batimastat decreases tyrosine phosphorylation of EGFR (see page 6238, right column and Figure 4), the statement "batimastat blocks EGFR tyrosine phosphorylation and batimastat plus EGF together increase tyrosine phosphorylation of EGFR" is correct. Furthermore, the feature of stimulation of a G protein or GPCR mediated extracellular signal transduction pathway by

batimastat alone, by EGF alone nor by batimastat plus EGF argued by applicant is not required for the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dong *et al.*, (May, 1999) as applied to claims 22-26, 28-31, 33-36, and 38 above, and further in view of Miyoshi *et al.*, (J. Biol. Chem., 272, 14349-14355, 1997).

The teachings of Dong *et al.*, have been summarized previously, *supra.*

Dong *et al.*, do not disclose that said precursor of the ligand for the receptor tyrosine kinase is proHB-EGF as recited in claim 27. .

Miyoshi *et al.*, do teach a cell line, AH66tc, that can produce proHB-EGF and contains EGFR (see abstract in page 14349, right column in page 14351, and Figure 4 in page 14352).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have used AH66tc to perform the method recited in claim 22 in view of the references of Dong *et al.*, and Miyoshi *et al.*, so that HB-EGF released from pro-HB-EGF can activate EGFR by binding to its extracellular domain. One having ordinary skill in the art would have been motivated to do so because the simple replacement of one kind of cell line that is capable to produce a ligand of EGFR (ie., a human mammary epithelial cell line that can produce EGF taught by Dong *et al.*,) from another kind of cell line that is capable to produce a ligand of EGFR (ie., AH66tc that can produce HB-EGF taught by Miyoshi *et al.*,) during the process of performing the method recited in claim 22 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the method steps of claim 22 since it is known that a variety of ligands such as HB-EGF in addition to EGF have been shown to stimulate EGFR and is released from their membrane-anchored precursors (see Dong *et al.*, page 6235, left column).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 11, second paragraph of applicant's remarks, applicant argues that "[M]iyoshi was cited for the disclosure of a cell line which produces proHB-EGF and contains EGFR. Miyoshi does not suggest or disclose modulating G-protein mediated signal transduction or a step of stimulating/disturbing the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims and thus does not cure the above discussed deficiencies in Dong".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection because Dong *et al.*, teach modulating G-protein mediated signal transduction or a step of stimulating/disturbing the G protein/GPCR initiated signal transduction pathway as required in the first step of the present claims as argued by applicant (see above rejection under 35 U. S. C 102 and above Response to Arguments on the rejection under 35 U. S. C 102).

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. No claim is allowed.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
November 12, 2004

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
11/15/04